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New device and method for prevention of nocosomial infections

The present invention concerns a device and method for reducing the incidence of nocosomial infections in humans and animals having an invasive medical device inserted into the body, in particular catheter-associated urinary tract infections. More specifically, the invention relates to a device having means for releasing low molecular antimicrobial compounds that permeates to the adjacent tissue and/or body cavity.

Background

Nocosomial infections are infections that are caught during a treatment or procedure performed in a hospital. Nocosomial infections are a major global concern that leads to increased hospitalisation, and sometimes even permanent debilities for the patient. In addition to the consequences for the patient, nocosomial infections may infect other patients and cause increased health care and hospital costs.

Major sources of nocosomial infections are insufficient sterilisation of medical equipment and unsatisfactory hygiene of the personnel at hospitals and other care centres and nursing homes. Outbreaks of nocosomial infection have been linked to a variety of non-sterile equipment like electronic thermometers and blood pressure cuffs.

Staphylococcus aureus is the most common cause of nocosomial infections and is of increasing concern because of the spread of methicillin resistant strains, which are refractory to treatment by most antibiotics. Examples of other microbial pathogens causing nocosomial infections are *Escherichia coli, Serratia marcescens, Klebsiella* and *Enterobacter* species and *Candida* species.

Venous catheters, urinary catheters, and ventilator-associated tubings are common sites and causes of nocosomial infections. Actually, catheter-associated urinary tract infection is the most common nocosomial infection and is, together with nosocomial pneumonia, two of the major causes of hospital-acquired infection, for which a substantial proportion of prescribed antibiotics is used.

Urinary catheterisation is a routine procedure in the hospital and chronic care settings and is associated with a significant risk of infection. The incidence of catheter-associated urinary tract infection (CAUTI) approaches 50 % after three days of continuous catheterization. The presence of a catheter within the urinary tract may also increase the difficulty of treating the infection. If a urinary catheter is left in place for long periods of time, bacteria will inevitably grow in it. A harmful infection may occur if the number of bacteria

becomes large or if specific pathologic bacteria grow in the urinary tract. Complications of CAUTI include bacteremia, pyelonephritis, urinary stones and renal failure with resulting morbidity and increased risk of death.

Most microorganisms, except *Staphylococcus aureus*, causing endemic CAUTI derive from the patient's own colonic and perineal flora or from the hands of health-care personnel during catheter insertion or manipulation of the collection system. Extraluminal contamination may occur early when the catheter is inserted or later by microorganisms ascending from the perineum by capillary action in the thin mucous film close to the external catheter surface. Intraluminal contamination occurs by reflux of microorganisms gaining access to the catheter lumen due to breakage in closed drainage or contamination of collection bag urine.

Most urinary catheters are equipped with an inflatable cuff situated near the catheter tip. The cuff keeps the catheter in place in the bladder after insertion. When inflated it represents the largest surfaces area of the catheter in the bladder. The outflow orifice of the catheter is situated distal to the cuff meaning that the cuff itself will be constantly embedded in residual urine. It is well known that urine is an excellent growth medium for urinary pathogens. Consequently, the cuff is a particularly vulnerable site for bacterial adherence and growth.

There is a heavy use of systemic antimicrobial drugs to treat and prevent nocosomial infections. Antimicrobial drugs probably keeps the rate of hospital-acquired infections at a considerably lower rate than it would be otherwise, but it unfortunately selects for resistant microorganisms causing many of the most severe nocosomial infections. Thus, there is a great need for new methods to prevent the occurrence and spread of nocosomial infections, both in an economical perspective but also from the patient's point of view.

Prior art

Most infected urinary catheters are covered by a thick biofilm containing the infecting microorganisms embedded in a matrix of host proteins and microbial exoglycocalyx. Biofilms may appear both intraluminally and extraluminally. Anti-infective-impregnated and silver-hydrogel catheters, which inhibit adherence of microorganisms to the catheter surface, significantly reduce the risk of CAUTI. However, those coated catheters mainly affect the infections caused by grampositive organisms or yeasts adhering to the surface of the catheter. Silver alloy and silver oxide coated catheters are also widely used to inhibit establishment of infection.

Other attempts to inhibit CAUTI are the use of anti-infective lubricants when inserting the catheter, soaking the catheter in anti-infective solution before insertion and continuously irrigating the catheterised bladder with anti-infective solution. Efforts have also been made to seal the connection between the catheter and collection tubing. None of these methods have given satisfactory results and new better ways to inhibit nocosomial infections would be valuable to replace or complement existing methods.

Nitric oxide (NO) is known for its role in the defence against microorganisms. US Patent Application No. 2002/0155174 describes the use of acidified nitrite as an antimicrobial agent for the treatment of viral diseases of the skin by topical application thereto. Acidified nitrite forms nitrous acid, which in turn dissociates to form oxides of nitrogen.

Nablo and Schoenfisch (J Biomed Mater Res, 67A: 1276-1283, 2003) also utilises the antibacterial properties of nitric oxide. They describe NO-releasing sol-gel coatings decreasing bacterial adhesion by 30 to 95% that, for example, can be used on implanted medical devices to prevent biofilm formation.

None of the above mentioned methods for preventing CAUTI relates to the cuff and preventing biofilm formation and bacterial growth on the surface of the cuff. For example, in silver coated catheters the inflatable cuff is not possible to coat and will remain a particularly susceptible site for infection.

In the present invention antimicrobial low molecular compounds are used to achieve an effective means to prevent establishment of nocosomial infections, in particular CAUTI.

Summary of the invention

The present invention relates to a device for insertion in a human or animal body and/or body cavity, said device having inflatable/expandable means for securing said device. The inflatable/expandable means comprises at least one component capable of releasing at least one low molecular antimicrobial compound (LMAC) in the device, said LMAC permeating to the adjacent tissue and/or body cavity.

The present invention also relates to a method for the prevention and treatment of nocosomial infections, such as CAUTI, originating from the insertion and/or use of a medical device in a human or animal. The method is characterized in that at least one component capable of releasing at least one LMAC is present in an inflatable/expandable

means of the device or administered into the device. The LMAC is capable of permeating to the adjacent tissue and/or body cavity.

Short description of the drawings

The present invention will be described in closer detail in the following description, examples, and attached drawings, in which

Fig. 1 schematically shows a double lumen urinary catheter having a hollow elongated body 1, an inlet/outlet 2 with a suitable fitting, and an inlet/outlet 3, also with a suitable fitting. The tip of the catheter has an opening 4, which is in fluid connection through a first lumen with the inlet/outlet 2. Slightly below the tip, a cuff 5 is provided. The cuff can be inflated through an opening 6, in fluid connection through a second lumen with the inlet/outlet 3.

Fig. 2 schematically shows the end part of any device 7 to be introduced into the body or a body cavity, and having a first lumen 8 for administering and a second lumen 9 for inflating / deflating a cuff delimited by an elastic membrane 10. The volume of the inflated cuff is indicated as 11.

Fig. 3 schematically shows a system for urine collection where a catheter 12 is inserted in a bladder 13. The residual urine volume is indicated as 14. The catheter is connected via connecting means 15 to a collection bag 17, containing a volume of urine indicated as 17. The capital letters A, B, C, and D indicated critical points of contamination and/or bacterial growth.

Fig. 4 shows the experimental set-up described in the example, where a sample of *E. coli* infected urine was placed in a 50 ml flask 19. An all-silicone catheter 18 was inserted in the flask, the cuff inflated with a solution according to one embodiment of the invention, and the flask turned up-side-down. The cuff efficiently sealed the neck of the flask and a volume of urine 20 was trapped in the flask.

Fig. 5 shows schematically two embodiments where the catheter tip is modified so that the LMAC will penetrate also to the inner lumen of the catheter and thus exert its antimicrobial effect on the urine collected from the bladder. In A the lumen wall has local areas of reduced thickness, here shown as wells in the catheter wall. In B the catheter wall is thinner at the section covered by the cuff, or part of said section.

Detailed description of the invention

Whenever a medical device comes in contact with a patient, a risk of infection is created. The risk of infection dramatically increases for invasive medical devices. The present invention provides a device and method for reducing the risk of nocosomial infections and for the treatment of nocosomial infections. Nocosomial infections may arise both inside and on the outside of an invasive medical device. Thus, the simultaneous reduction and elimination of microbial organisms both on the inside and outside of the device would be beneficial.

The present inventors surprisingly found that the use of low molecular antimicrobial compounds (LMAC's) could solve this problem. More specifically, the present invention relates to a device for insertion in a human or animal body and/or body cavity, said device having inflatable/expandable means for securing the device (Fig. 1 and 2), wherein the inflatable/expandable means comprise at least one component capable of releasing at least one LMAC in the device, said LMAC permeating to the adjacent tissue and/or body cavity.

The device of the present invention is an invasive medical device. An invasive medical device refers to any device wherein at least a portion of the device may be inserted percutaneously or into any site of the body of a human or an animal. Examples of medical devices includes urinary catheters, intratracheal tubes, vascular catheters, vascular catheter ports, wound drain tubes etc. In particular the present invention relates to a catheter for insertion into the urinary tract or an intratracheal tube for insertion into the respiratory tract of a human or animal body.

The LMAC released in the securing means of the device is a compound capable of permeating said means to the adjacent tissue and/or body cavity thereby exerting its antimicrobial effect both on the inside and on the outside of the device. Thus, the LMAC can be any antimicrobial compound, such as an antimicrobial gas, with sufficiently low molecular weight to permeate the device. In particular the LMAC is a reactive nitrogen intermediate (RNI), a reactive oxygen intermediate (ROI) or a combination of these two. Examples of LMAC's are, but not limited to, nitric oxide (NO), NO_2, N_2O_3, N_2O_4, HNO_2, HNO_3, NO^+, NO^-, O_2^-, O_3, singlet oxygen, H_2O_2, $OONO^-$, HOONO, OH radical and HOCl.

The inflatable/expandable means of the device can be any means for securing a medical device inserted into a human or animal body or body cavity. In the present invention the inflatable/expandable means consist of an elastic material of sufficient medical grade being permeable to gas but impermeable to water and which is expandable and inflatable to secure the device in the body. In particular the inflatable/expandable means is a cuff consisting of, but not limited to, elastic materials comprising polysiloxanes such as silicone

rubber comprising polydimethylsiloxanes, latex-free rubber, silicon-coated rubber or a semi-permeable or selectively permeable membrane such as Goretex®.

The LMAC's exert their antimicrobial effect unspecifically, which probably reduces the potential of the microorganisms to develop resistance to the LMAC's. The use of LMAC's with short half-lives in relatively high dose will further reduce the development of resistant bacteria. Furthermore, since some RNIs and ROIs are generated endogenously, the use of such compounds is unlikely to constitute any major health risk to the patient. Another advantage with the present invention is the local production of antibacterial compounds, which will not affect the normal microbial flora of, for example, the gut. The use of antibiotics in the inflatable/expandable means cannot exert the same antimicrobial effect as LMAC's since antibiotics can not permeate said inflatable/expandable means. Furthermore, the LMAC's permeating the said inflatable/expandable means will lead to high local concentrations of antimicrobial compounds leading to efficient biofilm prevention.

The LMAC of the present invention is released from at least one component comprised in the inflatable/expandable means. Said at least one component releasing the LMAC is any compound capable of releasing an antimicrobial compound with sufficiently low molecular weight to permeate the device. Examples of components that release RNIs/ROIs include, but are not limited to, S-nitrosothiols (low or high molecular-weight thiols), NONOates, nitroprusside, organic nitrate/nitrites, N-nitroso compounds, C-nitroso compounds, oximes, sydnonimines, oxadiazoles (furoxans), oxatriazoles, nitroxyl generating compounds (e.g pilotys acid), hydroxylamine, N-hydroxy-guanidines, nitrosylchloride, sodium azide, nitrosylhydrogensulphate, nitrosyltetrafluoroborat, dinitrosyl-iron-cysteine complex, etc.

There are several factors affecting the release of the LMAC. The RNIs/ROIs released by those compounds have different half-lives and differ in their pH dependency. Thus, the at least one component releasing the LMAC can be alternated depending on the special circumstances associated with the infection, the patient, where in the body the device is inserted etc.

Different LMAC's exert diverse effects on different bacteria. Thus, the present invention gives the possibility of using different LMAC's depending on the infectious bacteria. For example, *S. aureus* is sensitive to NO alone while *E.coli* is not. Furthermore, the LMAC's released can also be changed or modified with respect to the localization of the device since, for example, bacteria causing nocosomial infections coupled to the use of a urinary catheter might, at least partly, be distinct from the bacteria causing infections related

to the use of an intratracheal tube. Depending on the patient and the type of infection, the dosage of released LMAC can be changed or modified through the present invention. The term "changed or modified" as used above comprises changing the LMAC itself, e.g. by substituting one LMAC for another or using different combinations of LMAC's, or by changing the concentration(s) of the same.

In one embodiment of the present invention the LMAC is released when said at least one component is contacted with a second component. The second component can, for example, be an acid or base initiating the release of the LMAC when contacted with the component releasing the LMAC.

In another embodiment the component releasing the LMAC and the second component are present in the securing means as dry powders, granulaes, thin films or the like coating the inside of the cuff and the contact between the two components is accomplished through the addition of a liquid to said means. The liquid can for example be, but is not limited to, of water, saline or any physiological buffer, such as phosphate buffered saline (PBS) or the like.

In one embodiment of the present invention the at least one component of the device releasing the LMAC releases the LMAC upon acidification. The acidification is achieved through the addition of an acidifying agent (the "second component") reducing the pH in the device to about pH 1 - 5.5, preferably to about 2 - 4. The acidifying agent can be any acid reducing the pH in the device to the above-mentioned pH. Appropriate acids are for example, but not limited to, ascorbic acid, citric acid, acetic acid, butyric acid, diluted hydrochloric acid, diluted sulphuric acid, formic acid, nitrous acid or nitric acid.

In one embodiment of the present invention said at least one component is nitrite and said second component is an acidifying agent that, when brought into contact, release RNIs such as nitric oxide, N_2O_3 and nitrous acid.

In one embodiment of the present invention the means for securing the inventive device is at least one inflatable cuff situated somewhere along the device and the at least one component releasing the LMAC is present in said inflatable cuff. In another embodiment the second component is present in said inflatable cuff. In yet another embodiment both said at least one component releasing a LMAC and the second component are present in said inflatable cuff. The inflatable cuff has an arrangement for introducing said at least one component or said second component in the cuff. Said arrangement of the inflatable cuff making it possible to administer the component(s) repeatedly during the use of the device, thus more efficiently preventing or treating nocosomial infections during prolonged use of the

device in a patient. Said arrangement is also suitable for the introduction of a liquid into the cuff contacting the at least one component releasing a LMAC and the second component.

When the device is a catheter (Fig. 3) for insertion into the urinary tract of the human or animal body, the cuff, when the catheter is inserted, is situated in the urinary bladder surrounded by the residual urine present in the bladder. Thus, the LMAC's released by the present invention solves the problem with infections establishing on the outside of the cuff surrounded by the residual urine.

In one embodiment of the present invention the part of the device surrounded by the inflatable/expandable means have local areas of reduced thickness in order to allow the LMAC's to permeate also to the inside of the device thus exerting an antimicrobial effect also inside the device (Fig. 5A). According to another embodiment the catheter wall is thinner at a section surrounded by the inflatable cuff or a part thereof (Fig. 5B).

The present invention also relates to a method for preventing and/or treating nocosomial infections originating from the insertion and/or use of a device inserted into a human or animal body and/or body cavity, said device having inflatable/expandable means for securing the device, wherein at least one component capable of releasing at least one LMAC in said means is administered into said means, said LMAC permeates to the adjacent tissue and/or body cavity. In one embodiment of the present invention the method is used for reducing the risk of and treating nocosomial infections originating from the insertion and use of a urinary catheter. In another embodiment the method is used for reducing the risk of and treating nocosomial infections originating from the insertion and use of an intratracheal tube inserted into the respiratory tract of a human or animal body.

The inflatable/expandable means of the device can be any means for securing a medical device inserted into a human or animal body or body cavity. In the inventive method the inflatable/expandable means consists of an elastic material of sufficient medical grade being permeable to gas but impermeable to water and which is expandable and inflatable to secure the device in the body. In particular the inflatable/expandable means is a cuff consisting of, but not limited to, an elastic material consisting of or comprising polysiloxanes such as silicone rubber comprising polydimethylsiloxanes, latex-free rubber, silicon-coated rubber or a semi-permeable or selectively permeable membrane such as Goretex®. When the device is a urinary catheter the cuff, when inserted into the human or animal body, is situated in the urinary bladder surrounded by the residual urine present in the bladder.

The low molecular compound exerting the antimicrobial effect can be any antimicrobial compound with sufficiently low molecular weight to permeate the

inflatable/expandable means of the device wherein it is released. In particular the LMAC is a RNI, a ROI or a combination of these two. Examples of LMAC's are, but not limited to, nitric oxide (NO), NO_2, N_2O_3, N_2O_4, HNO_3, HNO_2, NO^+, NO^-, $O_2^{\cdot-}$, O_3, singlet oxygen, H_2O_2, $OONO^-$, HOONO, OH radical and HOCl.

The LMAC of the inventive method is released from at least one component comprised in the securing means of the device. Said at least one component releasing the LMAC is any compound capable of releasing an antimicrobial compound with sufficiently low molecular weight to permeate the device. Examples of components that release RNIs/ROIs include, but are not limited to, S-nitrosothiols (low or high molecular-weight thiols), NONOates, nitroprusside, organic nitrate/nitrites, N-nitroso compounds, C-nitroso compounds, oximes, sydnonimines, oxadiazoles (furoxans), oxatriazoles, nitroxyl generating compounds (e.g pilotys acid), hydroxylamine, N-hydroxy-guanidines, nitrosylchloride, sodium azide, nitrosylhydrogensulphate, nitrosyltetrafluoroborat, dinitrosyl-iron-cysteine complex.

In one embodiment of the method according to the invention the LMAC is released when said at least one component is contacted with a second component. The second component can, for example, be an acid or base initiating the release of the LMAC when contacted with the component releasing the LMAC.

In another embodiment of the method the component releasing the LMAC and the second component are present in the device as dry powders, granulaes, thin films or the like and the contact between the two components is accomplished through the addition of a liquid to the device. The liquid can for example be, but is not limited to, water, saline or any physiological buffer, such as phosphate buffered saline (PBS) or the like.

In yet another embodiment of the inventive method the at least one component releasing the LMAC releases the low molecular compound upon acidification. The acidification is achieved through the addition of an acidifying agent reducing the pH in the device to about pH 1 - 5.5, preferably to about 2 - 4. The acidifying agent can be any acid reducing the pH in the device to the above-mentioned pH. Appropriate acids are for example ascorbic acid, citric acid, acetic acid, butyric acid, diluted hydrochloric acid, diluted sulphuric acid, formic acid, nitrous acid, or nitric acid.

In another embodiment of the inventive method said at least one component is nitrite and said second component is an acidifying agent that, when brought into contact, release RNIs such as nitric oxide, N_2O_3 and nitrous acid.

In another embodiment of the present invention the method is for treatment of nocosomial infections in and around an inflatable cuff situated along the device. The at least one component and/or the second component is/are administered into the cuff situated along the device. The inflatable cuff has an arrangement (3 and 6 in Fig. 1) making it possible to administer said component that releases at least one LMAC and/or said second component to the cuff. Through the administrative arrangement of the inflatable cuff said component releasing a low molecular compound and/or the second component can be added to the device repeatedly during the use of the device, thus more efficiently preventing or treating nocosomial infections during prolonged use of the device in a patient. Said arrangement is also suitable for the administration of a liquid into the cuff contacting the at least one component releasing a LMAC and the second component. Furthermore, through the use of said arrangement it is easy to change or modify the dosage of the released LMAC in each individual patient.

The invention also relates to a method for the prevention and treatment of nocosomial infections, wherein a device as described above is used.

Urinary collection devices, such as containers or drainage bags, are generally used for collecting urine from a catheterized patient. A collection device usually has tubings that are attached to the catheter leading the urine to the collection device (Fig. 3). Catherization often results in the possibility of urinary tract infection resulting from growth of microorganisms in the collection device and the associated tubing. The microorganisms growing in the collection device might be transported back to the bladder when the collection system is moved or manipulated in association with breakage in closed drainage. There are four main critical points for establishment of infection during catheterization as indicated in Fig. 3. One is the area surrounding the opening of the urinary tract, indicated as A. Another is the inside of the bladder, B, where the cuff and the tip of the catheter reside in residual urine. A third point of infection is the connection or coupling C between the catheter itself and the collection device. In Fig. 3 the coupling C is drawn as situated closer to the catheter than to the collection bag. In reality, C could be at the collection bag, any where between the catheter and said bag, or in fact, several couplings C could be provided. The fourth critical point is the collection bag itself, D, where bacteria can grow in large volumes of urine at room temperature. There is a need for an effective method for the prevention of urinary tract infection originating from contaminants in the collection system.

Thus, the present invention also relates to a method for prevention of nocosomial infections in patients having a urinary catheter by preventing microbial growth in

the collection device coupled to a catheter wherein at least one component releasing a LMAC is added to the collection device. An advantage with the use of the inventive method is that the use of LMAC, exerting its antimicrobial effect unspecifically, most likely will have lower probability of giving rise to antibiotic resistant microbial strains. In particular the LMAC is a RNI, a ROI or a combination of these two. Examples of LMAC's are, but not limited to, nitric oxide (NO), NO_2, N_2O_3, N_2O_4, HNO_3, HNO_2, NO^+, NO^-, O_2^-, O_3, singlet oxygen, H_2O_2, $OONO^-$, HOONO, OH radical and HOCl.

The at least one component releasing the LMAC in the collection device is any compound capable of releasing a LMAC in the collection device, such as, but not limited to, S-nitrosothiols (low or high molecular-weight thiols), NONOates, nitroprusside, organic nitrate/nitrites, N-nitroso compounds, C-nitroso compounds, oximes, sydnonimines, oxadiazoles (furoxans), oxatriazoles, nitroxyl generating compounds (e.g Piloty's acid), hydroxylamine, N-hydroxy-guanidines, nitrosylchloride, sodium azide, nitrosylhydrogensulphate, nitrosyltetrafluoroborat, dinitrosyl-iron-cysteine complex.

In another embodiment of the method the at least one component releasing the LMAC in the collection device releases the low molecular compound upon acidification. The acidification is achieved through the addition of an acidifying agent ("the second component") reducing the pH in the device to about pH 1 - 5.5, preferably to about 2 - 4. The acidifying agent can be any acid reducing the pH in the device to the above-mentioned pH. Appropriate acids are for example ascorbic acid, citric acid, acetic acid, butyric acid, diluted hydrochloric acid, diluted sulphuric acid, formic acid, nitrous acid, or nitric acid.

In another embodiment of the inventive method said at least one component is nitrite and said second component is an acidifying agent that, when brought into contact, release RNIs such as nitric oxide, N_2O_3 and nitrous acid in the collection device.

The present invention also relates to a kit to be used for preventing or treating nocosomial infections originating from the insertion and/or use of an invasive medical device, such as a urinary catheter or intratracheal tube, having an inflatable cuff in a human or animal body and/or body cavity. Said kit comprises said device and a syringe suitable for inflating said cuff and said syringe comprises the necessary components for the release of a LMAC after administration of said components into said inflatable cuff of said device. The LMAC can be any compound with sufficiently low molecular weight to permeate the cuff and/or the device. In one embodiment the LMAC is a reactive nitrogen intermediate (RNI), a reactive oxygen intermediate (ROI) or a combination of these two. The kit is easy to use and there is

no need for additional equipment or special training of the personnel at hospitals or other health care centres.

The necessary components comprised in the syringe are at least one component releasing the LMAC and, optionally, a second component inducing the release of the LMAC upon contact with the LMAC releasing component. The component(s) can be present as dry powders, granulaes, thin films or the like that release said LMAC upon combination with a liquid such as water, saline or any physiological buffer, such as PBS. In one embodiment the powders and the liquid are kept in separate containers until combined in the syringe prior to administration.

In one embodiment of the inventive kit one of the necessary components in the syringe is nitrite that upon acidification produces RNIs. The acidification can for example be achieved through the addition of, but not limited to, ascorbic acid, citric acid, acetic acid, butyric acid, diluted hydrochloric acid, diluted sulphuric acid, formic acid, nitrous acid, or nitric acid.

The present invention can also be used in combination with other devices, methods and/or kits developed for the prevention and/or treatment of nocosomial infections, such as, bur not limited to, antiinfective lubricants that can be used when inserting the medical device, antiinfective creams or ointments applied to the device, soaking of the medical device in antiinfective antimicrobial-drug solution prior to use, silver oxide coated devices (e.g. catheters).

The present invention also relates to a device as described above exerting its antimicrobial effect on non-nocosomial infections. In one embodiment the at least one component releasing at least one LMAC is present in an inflatable cuff situated along a catheter inserted in the urinary tract of a human. The LMAC penetrates the cuff and exert its effect on the prostate. It has been suggested that for example chronic prostatitis is caused by a bacterial infection. By arranging a second cuff at a specific distance from the first cuff, securing the device, the second cuff can be positioned in the urinary tract so that it is surrounded by the prostate gland. This embodiment makes possible a long term, minimally invasive treatment of the prostate.

The present invention will now be further described in the following non-limiting example.

Example

Materials & Methods

An *E. coli* strain isolated from urine of a patient with lower urinary tract infection was used. A 50 ml glass bottle with a narrow neck (Fig. 4) was filled with fresh urine (pH 6.5) from a healthy volunteer. The urine was inoculated with the *E. coli* strain to a final density of 10^5 colony forming units/ml. Then an all-silicone urinary catheter was inserted in the bottle and the cuff was filled with a solution comprising:

1. Saline + ascorbate (20 mM) + HCl to a final pH of 2.0 (control; n=3)

or

2. Saline + ascorbate (20 mM) + HCl + sodium nitrite (2 mM), pH 2 (nitrite; n=3)

The expanded cuff was fixed at the neck of the bottle to prevent leakage of urine when the bottle was turned up-side-down. The glass bottle was then incubated in 37° C for 10 h after which growth of *E. coli* in the surrounding urine was monitored by optical density (OD) at 540 nm on a Spectramax® (Molecular Devices Inc.).

Results

In contols OD values increased from 0.12 to 0.35 while in the nitrite group, no visible growth was observed (OD 0.12 before and 0.13 after10 h).

The experiment shows that the addition of nitrite to an acidic ascorbate solution results in generation of bacteriostatic compounds (such as NO, N_2O_3 and nitrous acid), which can penetrate a thin silicone membrane and inhibit bacteria growing in urine outside the membrane.

Although the invention has been described with regard to its preferred embodiments, which constitute the best mode presently known to the inventors, it should be understood that various changes and modifications as would be obvious to one having the ordinary skill in this art may be made without departing from the scope of the invention which is set forth in the claims appended hereto.

Claims

1. A device for insertion in a human or animal body and/or a body cavity, said device having inflatable/expandable means for securing said device, **characterized in** that said inflatable/expandable means comprise at least one component capable of releasing at least one low molecular antimicrobial compound (LMAC) in the device, said LMAC permeating to the adjacent tissue and/or body cavity.

2. A device according to claim 1, wherein the LMAC is released when said at least one component is contacted with a second component.

3. A device according to claim 2, wherein said contact is accomplished through the introduction of a liquid selected from the group consisting of water, saline or any physiological buffer to said means.

4. The device according to claim 1, wherein said device is a catheter for insertion into the urinary tract of said human or animal and said means for securing said device is an inflatable cuff.

5. The device according to claim 4, wherein said cuff when inserted into the urinary tract is situated in the urinary bladder.

6. The device according to claim 1, wherein said device is an intratracheal tube.

7. The device according to claim 1, wherein said LMAC is a reactive nitrogen intermediate, a reactive oxygen intermediate or a combination of these two.

8. The device according to claim 1, wherein the LMAC is selected from the group consisting of nitric oxide (NO), NO_2, N_2O_3, N_2O_4, HNO_3, HNO_2, NO^+, NO^-, O_2^-, O_3, singlet oxygen, H_2O_2, $OONO^-$, HOONO, OH radical and HOCl.

9. The device according to claim 1, wherein said at least one component releasing a LMAC releases the LMAC upon acidification.

10. The device according to claim 9, wherein said at least one component is nitrite.

11. The device according to claim 1, wherein said at least one component releasing a LMAC releases the LMAC upon basification

12. A method for preventing and/or treating nocosomial infections originating from the insertion and/or use of a device inserted into a human or animal body and/or a body cavity, said device having inflatable/expandable means for securing said device, **characterized in** that at least one component capable of releasing at least one low molecular antimicrobial compound (LMAC) in said means is administered to said means, said LMAC permeating to the adjacent tissue and/or body cavity.

13. The method according to claim 12, wherein the LMAC is released when said at least one component is contacted with a second component.

14. The method according to claim 13, wherein said contact is accomplished through the introduction of a liquid selected from the group consisting of water, saline or any physiological buffer to said means.

15. The method according to claim 13 or 14, wherein said at least one component that releases a LMAC, said acidifying agent and/or said liquid is/are administered into said means for securing the device, said means having an arrangement for administering said component that release at least one low molecular antimicrobial compound, said acidifying agent in the cuff and/or said liquid.

16. The method according to claim 12, wherein said device is a catheter for insertion into the urinary tract of said human or animal body and said means for securing the device is an inflatable cuff.

17. The method according to claim 12, wherein said device is an intratracheal tube for insertion into the respiratory tract of said human or animal body.

18. The method according to claim 12, wherein said LMAC is a reactive nitrogen intermediate, a reactive oxygen intermediate or a combination of these two.

19. The method according to claim 12, wherein the LMAC is selected from the group consisting of nitric oxide (NO), NO_2, N_2O_3, N_2O_4, HNO_3, HNO_2 NO^+, NO^-, O_2^-, O_3, singlet oxygen, H_2O_2, $OONO^-$, HOONO, OH radical and HOCl.

20. The method according to claim 12, wherein said at least one component releases the LMAC upon acidification.

21. The method according to claim 20, wherein said at least one component is nitrite.

22. The method according to claim 12, wherein said at least one component releases the LMAC upon basification.

23. A method for the prevention and treatment of nocosomial infections, characterized in that a device according to any one of the claims 1-11 is used.

24. A method for the prevention of nocosomial infections in patients having an urinary catheter inserted by preventing microbial growth in the collection device coupled to an urinary catheter, **characterized in** that at least one component releasing at least one low molecular antimicrobial compound (LMAC) is added to the collection device.

25. The method according to claim 24, wherein said at least one component is nitrite that upon acidification releases a LMAC in the collection device.

26. The method according to claim 25, wherein the acidification is accomplished through the addition of an acidifying agent reducing the pH in the device to about pH 1 - 5.5, preferably to about pH 2 - 4.

27. A kit to be used in the prevention and/or treatment of nocosomial infections originating from the insertion and/or use of a invasive medical device having an inflatable cuff in a human or animal body and/or body cavity, said kit comprising said device and a syringe suitable for inflating said cuff, said syringe comprising the necessary components for the release of at least one low molecular antimicrobial compound (LMAC) after administration of said components into said inflatable cuff of said device.

28. A kit according to claim 27, wherein the device is a urinary catheter.

29. A kit according to claim 27, wherein the device is an intratracheal tube.

30. The kit according to claim 27, wherein said necessary components are present as powders that release said LMAC upon combination with a liquid such as water, saline or any physiological buffer.

31. The kit according to claim 27, wherein said necessary components are present as separate solutions that are combined prior to administration or simultaneously with the inflation of said cuff.

Abstract

The present invention discloses a device and a method for reducing the risk of hospital-acquired infections, nocosomial infections, originating from the insertion of the device and/or use of the device in the body of a human or animal. The invention in particular relates to a device releasing at least one low molecular antimicrobial compound permeating the device thereby exerting its antimicrobial effect also on the outside of the device.
(Fig. 3)
